

REMARKS

Claim Amendments

Claims 1, 2, 4, 6, 8, 9 and 14-16 are present in the application. Claims 3, 5, 7, and 10-13 are canceled. Claims 6, 8, 9 and 14-16 are now withdrawn. Claims 1, 2, and 4 are subject to examination. Claim 1 and 4 are amended.

Claim 1 is amended to provide that R_2 is selected from the group consisting of $-COOH$, $-OH$, $-NO_2$, $-OCH_3$, $-SO_3H$, $-SO_3^-$, and $-R_8-Y$, but does not include hydrogen; and to provide that Y is selected from the group consisting of carboxyl, carbonyl, amino, sulphydryl, thiocyanate, isothiocyanate, isocyanate, maleimide, hydroxyl, iodoacetamido, hydrazine, aldehyde, nitrophenyl, dinitrophenyl, and trinitrophenyl.

Claim 4 is amended to delete group formulas Ic and II.

Incorporation of Foreign Priority Claim

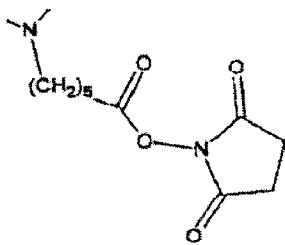
The Examiner continues to deny the foreign priority claim to PZ2003000002 on the basis that Applicant has not listed the priority claim in the first sentence of the specification or in an ADS, citing as authority MPEP 201.11.

In order to progress the prosecution of the present application, Applicant has amended the specification to list the foreign priority claim to PZ2003000002 in the first sentence of the specification.

Claim rejection under 35 USC §103(a)

Claims 1, 2, and 4 are rejected as obvious over Caputo (US2002/065421 or the "421 application") in view of Takashima et al (US2002/0051926 or the "926 application"), and Stavrianopoulos et al (US2003/0225247 or "247 application").

Applicant respectfully requests reconsideration of the rejection. Applicant calls to the Examiner's attention that R_2 has been amended to not include hydrogen, such that two functionalized linkers must be always present in the R_1 and R_2 positions. Furthermore, Claim 1 has been amended to provide that Y (in the group R_8-Y) has been limited to exclude from the group the "succinimidyl ester group", below, present for instance in formula 4a of the US '421 reference.



The compounds of present (and past) Claim 1 have two essential features: (1) they comprise always two functionalized linkers (i.e. having a terminal functional group capable of reacting) on the two indolenine ammonium atoms: R₁ and R₂ and (2) one of these linkers is always functionalized with an alkyne group: -C≡CH.

a. Insufficiency of Examiner's assertions in the Advisory Action

In the Advisory Action, the Examiner noted that the motivation for joining the cyanine dye to two desired target molecules through alkyne and another function group is suggested by “the previously cited references and the common knowledge at the level of one ordinary skilled in the art, which is bi-functional dye with heterobifunctional cross-linkers as a common commercial reagent by Pierce Chemical Company for example, and technical user manual Bioconjugate Techniques by Greg T. Hermanson under heterobifunctional cross-linkers.” The Examiner appears to have made these two references of record in support of the rejection, but the Examiner has not stated specifically where in the references the Examiner intends to rely for support for such rejection support, and has not provided copies of the references.

Consequently, Applicant respectfully requests that the specific disclosure(s) of the common commercial reagent by Pierce Chemical Company, and the technical user manual Bioconjugate Techniques by Greg T. Hermanson, be disclosed with sufficient specificity for Applicant to review in order to respond, along with the date on which it became available as prior art. Applicant also requests that the Examiner send copies of the respective references to Applicant for review.

Applicant also requests that the Applicant be given additional time, after the Examiner has sent the above reference documents to Applicant, in order for Applicant to prepare any supplemental response.

b. The US '421 reference

First of all, none of the disclosed compounds in US '421 contains at the same time two functionalized linkers in the positions corresponding to R₁ and R₂ of the present Claim 1. Second, none of the disclosed US '421 compounds contain one linker, in a position corresponding to either R₁ or R₂, that is functionalized with a -C≡CH group.

US '421 claims and describes asymmetrical indocyanines compounds having always only a single functionalized linker, which therefore is capable of bonding only one molecule (either a biomolecule or a dye). If one looks in US '421 at formula (I) of claim 10, or at any one of the compounds of claim 11, or at any one of the compounds of claim 14, or even at any one of the compounds illustrated in figures 4 to 11, one realizes immediately that when one substituent on either of the two indolenine ammonium atoms is functionalized, the other is not functionalized: namely it is a simple ethyl group (-CH₂-CH₃), which is well known to be inert.

Moreover, when one functionalized linker is present on the benzyl ring of one of the indolenine moiety, then neither of the two indolenine ammonium atoms, corresponding to the present R₁ and R₂ positions, is functionalized, both bearing an inert ethyl group.

c. "Reactivity" of the moieties

The Examiner also contests Applicant's argument that the '421 application teaches away, by questioning "First, if a compound with 'carboxylalkyl or sulfonatoalkyl chains or electron withdrawing groups in the benzene ring' would decrease the reactivity of the indolenines, why the instant application claims the such less active compound as the Formula (Ic) in claim 4 for the same application?"

The Applicant has clarified that the issue of reactivity of the indolenine moiety in the '421 reference pertains to the synthesis reaction of the compound, and not to the reactivity of the linkers to biomolecule or a second dye molecule. This synthesis reactivity was relevant to understand the scope of the US '421 because, as understood by a person of ordinary skill, the '421 application relates to asymmetric indocyanine dyes (see for example Claim 14). Since the final molecule is obtained by reacting a first indocyanine moiety with a second different indocyanine moiety, if the reactivity of the two moieties is different, the synthesized amount of the desired asymmetrical indocyanines "heterodimer" is much lower than the amount of the symmetrical "homodimer". For this reason, selection of the chains or electron withdrawing

groups in the benzene ring became a relevant concern in the '421 application. A person of ordinary skill would understand that the reactivity of the groups during synthesis would be different because the indocyanine dyes of the '421 reference are asymmetric. A person of ordinary skill would not consider that the compounds of the '421 reference are intended to include symmetrical compounds.

d. The US '247 and the US '926 references

Likewise, all of the compounds disclosed in the description, claims and figures of the US '247 and the US '926 references are "monofunctional" having only one linker, or in the case of the US '926 reference, two identical functionalized linkers. One cyanine molecule can react with one biomolecule only. This is evident for example from paragraph [0135] of the US '247 reference where it is clarified that "*R₁-R₈ comprises a reactive group that could be used to join the cyanine dye to a desired target molecule*". The person of ordinary skill would read in the US '247 that all of the claims were directed to the labelled biomolecule (target molecule T), and define always a 1:1 ratio between the target molecule (T) and the marker molecule (M), and would see from figure 5 and 6 that the marker (either D, energy donor or A, energy acceptor) is always bonded to one single biomolecule (T). Thus, there is no express or inherent description or suggestion of joining the cyanine dye to two desired target molecules.

Therefore, the skilled person could not find in either US '247 or US '926 any express teaching, suggestion or motivation to produce a cyanine modified compound as claimed in present Claim 1, usable as a bridge between two biomolecules, or between a biomolecule and a second dye molecule.

The Examiner also states that both the US '247 and US '926 teach a cyanine compound that has an alkyne (-R1≡CH) attaching to the cyanine core moiety, used as a dye and a probe for labeling biomolecules, respectively. Applicant disagrees. Literally, both the US '247 and US '926 teach a substituent "R" which can be selected from a group of substituents, one of which may be alkyne. The Examiner has not disclosed where in the references a motivation can be found for one to select the alkyne substituent from among the several other substituents in the group, nor is the selection of the alkyne moiety "obvious to try".

Consequently, the Examiner has failed to establish a *prima facie* case of obviousness, or in the alternative has failed to rebut Applicant's traversal of the same.

Therefore, the compounds of Claims 1, 2 and 4 are patentably distinct from the compound of US '421, further in view of the '926 application and the '247 application.

Double patenting

The Examiner has rejected Claims 1, 2, and 4 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-11 of US Patent 6,136,612 (the '612 patent).

Applicant traverses.

At the outset, Applicant requests that the Examiner review the date of publication of the '612 patent, and confirm that the rejection is only a double patenting rejection.

Present Claim 1 necessarily requires, as an essential feature, that the two linkers in R_1 and R_2 be functionalized by different reacting groups: the former being always $R_1\text{-C}\equiv\text{CH}$, the latter never comprising the alkyne group (- $\text{C}\equiv\text{CH}$). Accordingly, the two linkers have different reactivity.

Actually, it is specifically indicated in paragraph [0012] of the present application that when more than one functionalized linker is present, undesired cross-linking between multiple similar molecules, undesired multiple reactions or purification problems occur.

Since the aim of the molecules of Claim 1 is to link two different ligand-molecules (either two different biomolecules or a biomolecule and a second dye), the presence of two different functionalized linkers avoids the above indicated problems.

US '612 discloses indocyanine fluorescent dyes comprising two functionalized linkers in position R_1 and R_2 . As immediately evident, the two linkers are always disclosed as being functionalized with the same, identical reacting group, one selected from "-COOH, phthalimido", etc. See, by example, Claims 1, 7 to 11 and columns 7, 12, and 14.

If the person ordinarily skilled in the art wished to improve the availability of the reacting groups, and if he/she, as alleged, found in US '926 a suggestion to use an alkyne group, such as - $\text{C}\equiv\text{CH}$, then nevertheless by following the teaching in the US '926 reference, he/she would only have envisaged cyanine molecules having two identical linkers. In fact US '926 (as does US '612) discloses indocyanine molecules having either two identical functionalized linkers or only one functionalized linker. See paragraph [0084] and the compounds on pages 7, 8, 9 and 10, and in Claims 1 and 2. In other words, the skilled person would not have found in US '926 any

motivation or reason to use two differently functionalized linkers.

Also, US '247 discloses, among many various other possible substituents, linkers functionalized with an alkyne group, namely -C≡CH. Yet US '247 discloses molecules having only one linker. Therefore, if the person of ordinarily skill would have perhaps found in this document some hint to use a -C≡CH functional group, he/she would not have found in this document any motivation to have two different functional linkers.

In conclusion, the Examiner has failed to establish a *prima facie* case of obviousness in view of US '612, or in the alternative, the Examiner has failed to rebut Applicant's traversal of the same.

Therefore, the compounds of Claim 1, 2 and 4 are patentably distinct from the compound of US '612, further in combination with US '926 or US '247, and none of the cited references provide any disclosure or suggestion to provide two different linkers having different functionalization. The compounds of Claim 1, 2 and 4 are therefore patentable over the US '612 reference in view of the US '926 and/or US '247 references.

Claim Objections

The Examiner had objected to Claims 1, 2, and 4 as containing both elected and non-elected subject matter.

Applicant understands that, should the elected subject matter be allowed, the Examiner would extend examination to the non-elected embodiments contained in New Group II. In view of the present amendments and arguments, the elected subject matter appears to be patentable over the prior art of record, and Applicant requests that the remaining non-elected subject matter of the claims be examined.

CONCLUSION

Applicant believes a full and complete response to the Final Action has been made. In view of the above remarks that traverse the rejections, allowance of all the claims is respectfully requested.

Respectfully submitted,

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